Acute renal transplant rejection following nivolumab therapy for metastatic melanoma

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TITLE OF CASE

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SUMMARY

Background: Cancers can develop the ability to evade immune recognition and destruction. Immune checkpoint inhibitors (ICIs) are drugs targeting these immune evasion mechanisms. ICIs have significantly improved outcomes in several cancers including metastatic melanoma. However, data on toxicities associated with allograft transplant recipients receiving ICI is limited.

Case: We describe a case of a 71-year-old female who was diagnosed with metastatic melanoma 13 years after renal transplantation. She was commenced on the immune checkpoint inhibitor Nivolumab. She developed acute renal transplant rejection 15 days after administration of the first dose. She continues on haemodialysis but has demonstrated complete oncological response.

Discussion: This case demonstrates the risk of acute renal transplant rejection versus improved oncological outcomes. Patients and clinicians must consider this balance when initiating ICI therapy in allograft transplant recipients. Patients should be fully consented of the potential consequences of acute renal transplant rejection including life-long dialysis.

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BACKGROUND

Allograft transplant recipients commonly receive immunosuppressive drugs to reduce the risk of transplant rejection. These drugs decrease immunosurveillance and result in activation of oncogenic viruses, contributing to an increased risk of developing cancer.[1] Examples of such viruses include the human papillomavirus, Ebstein-Barr virus, hepatitis B virus and hepatitis C virus.[2] It is estimated that renal transplant recipients have a 3-5 times increased risk of developing lung cancer, colorectal cancer, melanoma and non-melanoma skin cancers, particularly squamous cell cancer.[3][4]

In addition to the original six Hallmarks of Cancer, Hanahan and Weinberg subsequently described the evasion of immune destruction as a further hallmark.[5] In a healthy individual, cytotoxic natural killer cells and T cells are responsible for the recognition of, and subsequent immune response against tumour cells.[6] However, some cancers develop mutations granting the ability to evade immune recognition and consequent immune-mediated apoptosis.[7] Upregulated expression of programmed cell death ligands (PD-L1 and PD-L2) have been observed in several cancers including melanoma.[3] These ligands bind to PD-1 receptors on T-cells and cause T-cell inhibition. Similarly, an increased expression of cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) on cancer cells can result in the inhibition of T-cell function.[8] With this protection from the immune system, cancer cells can proliferate unchecked.

Immune checkpoint inhibitors (ICIs) are anti-cancer therapies that target these immune cell recognition pathways. Nivolumab and pembrolizumab are monoclonal antibodies that bind to the PD-1 receptor on T-cells, preventing its interaction with PD-L1 and PD-L2 ligands on cancer cells. This inhibits the ability of a cancer cell to evade recognition by host T-cells.[9][10] Ipilimumab is another monoclonal antibody that blocks CTLA-4 signalling, allowing physiological T-cell responses.[11]

ICIs have revolutionised the treatment of several cancers including metastatic melanoma. Both single agent and combination therapy are effective in this setting, with five-year survival reported as 52% in the CheckMate 067 study of combination ipilimumab with nivolumab.[12]

However, the use of ICIs is associated with immune-mediated adverse reactions (IMARs). These adverse reactions can be organ-specific or organ non-specific. Organ-specific toxicity can resemble autoimmune disease and is due to an enhanced activity of the immune system.

Examples of such reactions include endocrinopathies, colitis, , nephritis and pneumonitis.[13][14][15] The risk and consequences of IMARs are more significant in allograft transplant recipients. The stimulation of immune activity caused by ICIs increases the risk of the transplanted organ being recognised as foreign This can ultimately lead to transplant rejection. Therefore, care must be taken when considering ICI therapy in allograft transplant recipients.

We present a case from our unit where a renal transplant recipient opted to receive an ICI following a diagnosis of metastatic melanoma.

CASE PRESENTATION

A 71-year-old female with renal failure secondary to primary chronic pyelonephritis received a living unrelated donor kidney transplant in 2003. Her immunosuppressant therapy for transplant rejection prevention was mycophenalate mofetil, tacrolimus and prednisolone at this time.

She then presented with an enlarging non-ulcerating left scalp lesion in 2016. This was subsequently diagnosed as a Breslow thickness 1.6mm superficial spreading malignant melanoma. She underwent a wide local excision, burring of outer cortex of skull and split skin grafting in the same year. Due to the location of the lesion, the medical team decided not to perform a sentinel lymph node biopsy at this stage.

In October 2017, she was diagnosed with a second melanoma – on this occasion an ulcerating Breslow thickness 2.3mm lentigo maligna melanoma on her left temple. This was also excised. A staging computed tomography (CT) scan at this time showed a nodule of unknown significance in the left lung upper lobe. Another CT scan 4 months later demonstrated 2 new coalescent nodules in the right lung middle lobe while the left lung upper lobe nodule from the previous scan remained unchanged. Her case was reviewed at the local tumour board and the consensus was that this was likely in keeping with metastatic spread from a melanoma primary. Therefore, she did not have a biopsy of the lung lesions or a PET-CT at this stage and the decision was made to monitor closely with repeat imaging.

In July 2018, the patient developed left neck lymphadenopathy. A new 1.2cm malignant level V neck node and a new 6mm left lung lower lobe nodule suspicious for metastasis was noted on repeat CT scan. Her previously noted lung lesions were stable. She underwent a left neck levels II-V nodal dissection. 3 of the 55 dissected lymph nodes tested positive for metastatic melanoma which was wild type for BRAF, Kit and NRAS. At this stage, her immunosuppressant therapy consisting of mycophenalate mofetil, tacrolimus and prednisolone was reduced to tacrolimus (1.5mg, twice daily) and prednisolone (5mg, once daily) in an attempt to slow disease progression.

In November 2018, she then developed 4 nodules on her scalp. These nodules were completely excised, with 2 of the nodules showing recurrence of melanoma. BRAF testing was discussed at the local tumour board but it was felt that the recurrence was consistent with the surgical

specimen 4 months prior; BRAF re-testing was therefore not re-performed. Systemic treatment with the PD-1 inhibitor nivolumab for metastatic melanoma was considered at this point. As the patient was clinically well, with a slow rate of disease progression and ICI therapy would potentially have a high risk of renal transplant rejection, the decision was taken to manage conservatively and observe closely after discussion with the patient.

However, by May 2019, the patient had further disease progression with new scalp nodules, an enlarged parotid lymph node and an increased number and size of pulmonary nodules. As the disease was gathering pace, it was agreed to commence ICI therapy in the form of nivolumab, 480mg every 4 weeks.

Prior to commencing immunotherapy, her baseline creatinine was 100umol/L and urea was 7.5mmol/L. 15 days after the 1st dose of treatment, she developed oliguria, shortness of breath, bilateral pedal oedema and a 3kg weight gain. Blood tests showed that creatinine had risen to 392umol/L and urea to 19.2mmol/L (Figure 1), corresponding to acute kidney injury stage 3. The patient was diagnosed with acute renal transplant rejection and commenced on haemodialysis. Her tacrolimus was stopped but she remained on prednisolone to reduce symptoms of transplant rejection.

INVESTIGATIONS *If relevant*

NA

DIFFERENTIAL DIAGNOSIS *If relevant*

NA

TREATMENT *If relevant*

NA

OUTCOME AND FOLLOW-UP

The patient continued with her nivolumab regime post-transplant rejection. Imaging after 7 cycles of nivolumab therapy showed complete response to therapy with a resolution of the pulmonary nodules (Figure 2) and resolution of the 2 scalp nodules (Figure 3 and Figure 4). This response is ongoing. She did not experience any adverse skin effects during her nivolumab treatment. Interruption of her therapy was discussed at length, but the patient expressed her wish to continue receiving her therapy. She will complete a 2-year course of nivolumab in March 2021. She remains on low-dose prednisolone and 3-times-a-week haemodialysis.

DISCUSSION *Include a very brief review of similar published cases*

Before the introduction of ICIs, prognosis for advanced melanoma was poor. Patients treated with dacarbazine and interleukin-2 had a median overall survival (mOS) of 11.2months and 19.6months respectively.[16][17] However, trials have proven the higher efficacy of ICIs in the management of melanoma.

The CheckMate 067 trial demonstrated that for patients receiving nivolumab alone for stage III or IV melanoma (with or without BRAF mutations), the overall 5-year survival was 44% and mOS was 36.9months.[12] The same trial also demonstrated that for patients receiving the combination of nivolumab with ipilimumab, the mOS was 60.0months and the overall 5-year survival was 60% in tumours with BRAF mutation and 48% in tumours without BRAF mutation. The combination arm was associated with significantly higher levels of IMARs. 22% of these patients had complete oncological response, 36% had partial response and 12% had stable disease.[12] The KEYNOTE-001 trial demonstrated that pembrolizumab alone in advancedmelanoma achieved a mOS of 23.8months and an overall 5-year survival of 34%. 16% of patients in this trial had complete response, 25% had partial response and 24% had stable disease.[18] Studies comparing nivolumab with pembrolizumab have shown a mOS of 23.9months with nivolumab compared to 22.6months with pembrolizumab [19]

The aforementioned trials excluded transplant recipients in their study, and therefore data on toxicities in this patient group is derived primarily from case reports and series.

We describe a case of acute renal transplant rejection requiring dialysis after commencement of nivolumab for metastatic melanoma. The onset of rejection was approximately 15 days post cycle 1, despite ongoing tacrolimus and prednisolone immunosuppression. The patient has

subsequently had complete oncological response and continues on her nivolumab therapy. This case adds on to a growing number of cases involving renal transplant recipients receiving ICI therapy for metastatic melanoma. Table 1 compares our case with other previously reported cases.

A study by Manohar et al. showed that 8/18 (44.4%) renal transplant recipients treated with nivolumab alone experienced rejection. This was compared to 3/18 (16.6%) patients who were treated with pembrolizumab alone and 2/18 (11.1%) with ipilimumab alone. Median time from ICI initiation to acute renal transplant rejection in this study was 24 days. Of these 18 patients whom developed acute renal transplant rejection after ICI therapy, 9 (50.0%) patients had favourable response (stable disease, partial response and complete response) while 7 (38.9%) patients had progressive disease. This is compared to patients whom did not develop acute renal transplant rejection after ICI therapy where 11/25 (44.0%) had favourable response and 14/25 (56.0%) had progressive disease.[28] The connection between oncological response and incidence of IMARs as shown by this study has similarly been demonstrated by Indini A et al. This study correlated the incidence of IMARs with improved progression free survival. Median overall survival for patients who experienced IMARs was 21.9months, as compared to 9.7months in patients who did not experience IMARs.[29]

Fisher et al. reported that 7/11 (64%) patients experienced acute renal transplant rejection when treated with nivolumab alone. 2/8 (25%) acute renal transplant recipients treated with pembrolizumab and another 2/8 (25%) treated with ipilimumab alone also had acute renal transplant rejection.[30]

Another study by Smedman et al. showed that 4/7 (57.1%) renal transplant recipients treated with PD-1 inhibitor alone had acute transplant rejection. This was the same for 1/3 (33.3%) renal transplant recipients treated with ipilimumab alone.[31]

Abdel-Wahab et al. demonstrated that 2/5 (40.0%), 4/9 (44.4%) and 2/4 (50.0%) renal transplant recipients had acute transplant rejection when treated with Nivolumab, pembrolizumab and ipilimumab alone respectively.[29] The median time from ICI initiation to acute renal transplant rejection were 18.5 days for nivolumab alone, 21 days for pembrolizumab alone and 21 days for ipilimumab alone.[32]

Our patient's experience follows closely with the results of the above studies. The higher incidence of acute transplant rejection associated with nivolumab demonstrated by the studies corresponds with the acute transplant rejection in our patient after nivolumab initiation. Our patient also had complete oncological response, tallying with the higher percentage of patients having both IMARs and favourable oncological response. Our patient developed acute transplant rejection 15 days after ICI initiation, similar to the 18.5 days demonstrated by Abdel-Wahab et al.

Since the decision to continue treatment was made, new evidence has been published showing the efficacy of interrupting treatment early in patients achieving complete oncological response. The KeyNote-006 trial demonstrated that patients who achieved complete oncological response and received 2 years of pembrolizumab treatment had an estimated 24-month progression free survival (PFS) of 85.4%. In those who achieved complete oncological response but received less than 2 years of pembrolizumab (6 months of pembrolizumab and 2 additional doses after first scan showing complete response) PFS was 86.4%.[33] This highlights the durability of response in patients who have a complete oncological response and provides reassurance to clinicians and patients about treatment interruption if required.

In summary, patients with organ transplants appear to have a high chance of organ rejection with use of ICI, but this comes with a greater chance of oncological response. This case and the other published reports highlight the importance of an individualised discussion with each patient, enabling an informed treatment decision to be made.

Case	Immune checkpoint inhibitor	Age	Sex	Kidney disease	Kidney transplantation	Melanoma diagnosis (year diagnosed)	Site of metastases (year diagnosed)	Immunosuppression before initiation of ICI	Allograft rejection	Time interval from ICI to rejection	Treatment duration	Treatment response
This case	Nivolumab alone	71	F	Chronic primary pyelonephritis	2003	1.6mm superficial spreading melanoma (2016)	Lung and scalp	Tacrolimus and prednisolone	Acute T-cell mediated rejection	15d	Ongoing	Complete response
Ong et al.[20]		63	F	Hypertension and diabetes mellitus	2004	2.59mm melanoma	Lung and hilar lymph nodes	Prednisolone	Acute T-cell mediated rejection	8d	Ongoing	Partial response
Winkler et al.[21]		60	F	Polycystic kidney disease	2003	Metastatic melanoma (2014)	Lung, brain and intrathoracic lymph nodes (2016)	Prednisolone and mycophenalate mofetil	No rejection	NIL	4 doses	Disease progression
Tio et al.[22]		48	M	NR	NR	Metastatic melanoma	NR	Tacrolimus and prednisolone	Acute T-cell mediated rejection	NR	1 dose	Partial response
Deltombe et al.[23]		73	M	NR	NR	Superficial spreading melanoma	NR	Everolimus	Acute T-cell mediated rejection	85d	2 doses	Disease progression
Winkler et al.[21]	Pembrolizumab alone	58	M	Hydronephrosis	1982	Uveal melanoma (2013)	Lung, liver and bone (2015)	Cyclosporine	No rejection	NIL	4 doses	Disease progression
Kwatra et al.[24]		58	M	IgM nephropathy	2001	21mm ulcerated nodular melanoma	Liver, bone, hilar lymph nodes and porta hepatis lymph nodes	Azathioprine and everolimus	Rejection	42d	2 doses	Disease progression
Tio et al.[22]		70	M	NR	NR	Metastatic melanoma	NR	Tacrolimus and prednisolone	No rejection	NIL	NR	Disease progression
Tio et al.[22]		75	M	NR	NR	Metastatic melanoma	NR	Prednisolone	No rejection	NIL	NR	Partial response
Tio et al.[22]		65	M	NR	NR	Metastatic melanoma	NR	Prednisolone, mycophenalate mofetil, tacrolimus	No rejection	NIL	NR	Disease progression
Winkler et al.[21]		58	M	Hydronephrosis	1982	Uveal melanoma (2013)	Lung, liver and bone (2015)	Cyclosporine	No rejection	NIL	4 doses	Disease progression
Lipson et al.[25]	Ipilimumab alone	72	M	Hypertension	2000	8mm ulcerated melanoma (2008)	Left axillary lymph nodes	Prednisolone	No rejection	NIL	NR	Complete response
Lipson at al.[25]		58	M	Polycystic kidney disease	2004	4.2mm nodular melanoma (2011)	Lung, right neck lymph nodes and mesenteric lymph nodes	Prednisolone	No rejection	NIL	4 doses	Disease progression
Jose et al.[26]		40	M	NR	1997	Ocular melanoma (2013)	Liver (2013)	Prednisolone	Acute T-cell mediated rejection	NR	2 doses	Disease progression
Zehou et al.[27]		67	M	Nephroangiosclerosis and diabetes mellitus	2012	Metastatic melanoma (2014)	Lymph nodes	Everolimus	No rejection	NIL	4 doses	Disease progression
Zehou et al.[27]		57	F	Polycystic kidney disease	2007	Lentigo malignant melanoma (2010)	Lymph nodes	Sirolimus and prednisolone	No rejection	NIL	NR	Disease progression
Zehou et al.[27]		68	F	Polycystic kidney disease	2001	Metastatic melanoma	Lung, liver, bone and lymph nodes	Everolimus and prednisolone	No rejection	NIL	2 doses	Disease progression

Table 1: Case reports of renal transplant recipients receiving ICI therapy for metastatic melanoma. NR=Not reported

LEARNING POINTS/TAKE HOME MESSAGES *3-5 bullet points*

- Immune checkpoint inhibitor therapy has greatly improved metastatic melanoma outcomes.
- Renal transplant recipients risk acute renal transplant rejection when receiving immune checkpoint inhibitor therapy.
- Clinicians must consider the risk of acute renal transplant rejection alongside the benefit of improved oncological outcomes with immune checkpoint inhibitors.
- Patients should be fully consented of the potential consequences of acute renal transplant rejection including life-long dialysis before deciding to initiate ICI therapy.

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FIGURE/VIDEO CAPTIONS

Figure 1: Changes in Creatinine from baseline to post-acute renal transplant rejection

Figure 2: CT scan of the lungs before Nivolumab (A) and after 7 cycles of Nivolumab (B). A 15mm lung nodule in the left lung lower lobe (arrowed) has resolved within this period.

Figure 3: CT scan of the head before Nivolumab (A) and after 7 cycles of Nivolumab (B). A 22mm lesion in the left occipital region (arrowed) has resolved with some scarring within this period.

Figure 4: CT scan of the head before Nivolumab (A) and after 7 cycles of Nivolumab (B). A 6mm lesion in the posterior midline of the scalp (arrowed) has completely resolved within this period.

PATIENT'S PERSPECTIVE

Q: How was your journey from the very beginning, from the melanoma diagnosis?

A: I wasn't frightened at the initial diagnosis of the melanoma; it was very quickly cut out from the top of my scalp. I was only really worried when it spread to my lymph nodes, worried that it might have spread elsewhere. It was also scary when my neck blew up after the operation and when I went to the ICU. I was a bit more assured when the doctors told me that only 3 out of 55 of the lymph nodes were infected. I was initially told that I had 3 to 6 months to live if I didn't go for the immunotherapy. I still wanted to be around with kids and it felt like there was no choice but to go for the immunotherapy.

There was some trauma with the rejection, but I was aware and open to dialysis. I felt that it was an acceptable risk compared to only having 3 to 6 months to live. There is some regret about the rejection with how I'm living my life now, mainly because of the breathlessness. I can't walk short distances anymore without feeling breathless and needing to sit down. It's definitely lowered my quality of life a bit, but I am very thankful for my husband for helping me around. Just last week I had around 1.5 litres of fluid drained from my lungs. This was after the doctors were trying to drain fluid everywhere else that was not there. I felt much better after taking off the fluid, but I feel that it's coming back again.

I am not someone who thinks too much of the future, I prefer to take it one day at a time and live in the now, but there is definitely some anxiety of the unknown.

My brother died of neck cancer, back when there was no immunotherapy. I thought that it was really scary and I didn't want to go through it without trying the immunotherapy. I see immunotherapy as hope.

Q: Would you 'recommend' immunotherapy to people like you?

A: Yes, I would 'recommend' it. The diarrhoea I had was problematic but bearable in the end. I think I was very lucky with the side effects in the way that it's not as bad as some people.

Q: How would you describe your journey?

A: Definitely rocky with its up and downs

Q: If you were to go back to 2016, back to the beginning, would you have done anything differently? Would you have asked for anything differently?

A: Not at all. I am very happy with the care I have been provided, the staff and my entire journey. I've got no complains whatsoever. And no, I don't think I would have done anything differently. I feel very supported

Q: Do you feel that the rejection was worth it?

A: Yes, it was worth the rejection. I am ok with the dialysis 3 times a week; I am managing well with this"

Q: What went through your mind during the period of rejection?

A: I thought it was over and I actually wished it was over; I wasn't sure I was able to cope with it anymore, with one thing coming after another."

Q: What are your prospects for the future from today onwards?

A: I'm hoping to continue to get away on weekends, go for walks once in a while. I am very lucky to have my husband who pushes me, encourages me, and who is a good support. I want to continue getting hugs from my grandchildren. Life is too short to give up. I have a tremendous amount of support too from my faith. It may be silly to some people the amount of support I get from my faith, but it is very important to me.

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